Response Serial No. 09/518,501 Page 4 of 110

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p$ -OR¹², and $-(CH_2)_p$ -SR¹²;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic; each R¹ is independently selected from the group consisting of alkyl, aryl, and aralkyl or together R¹ and R¹ form a cyclic group, optionally containing a heteroatom;



Response Serial No. 09/518,501 Page 5 of 110

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

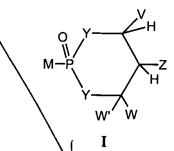
 R^{12} is selected from the group consisting of -H, and lower acyl; one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻, or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or –N(lower alkylhalide);
 - 2) R⁶ is not lower alkylhalide; and
 - 3) R^1 is not methyl.

167. (New) The method of making a compound of formula I:



comprising converting a hydroxyl or an amino on M to a phosphate or phosphoramidate, respectively, by reaction with L'-P(O)(-YCH(V)CH(Z)-CW(W)Y-)

wherein L' is a leaving group selected from the group consisting of -NR¹₂, aryloxy, and halogen; V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or

Response Serial No. 09/518,501 Page 6 of 110

aryloxy arbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and W must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH $\stackrel{?}{=}$ CR²₂)OH, -CH(C $\stackrel{?}{=}$ CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCO₂R², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

By

Response Serial No. 09/518,501 Page 7 of 110

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻, or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom:

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), –N(lower alkylhalide)₂, or –N(lower alkylhalide);
 - 2) R⁶ is not lower alkylhalide;
 - 3) both R¹ groups are not benzyl or ethyl at the same time.
- 168. (New) The method of claim 167 wherein L'-P(O)(-YCH(V)CH(Z)-CW(W')Y-) is a single stereoisomer.
- 169. (New) The method of claim 168 wherein said stereoisomer is generated using a chiral amino alcohol.

170. (New) A compound, R¹₂N-P(O)(-YCH(V)CH(Z)-CW(W')Y-), wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

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Response Serial No. 09/518,501 Page 8 of 110

aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

 $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C≡CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p$ -OR¹², and $-(CH_2)_p$ -SR¹²;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-R^2$, then at least one of X, W, and W' is not -H, alkyl, aralkyl, or alicyclic; each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl; or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom; with the proviso that both R^1 groups are not benzyl or ethyl at the same time; and R^2 is selected from the group consisting of R^3 and -H;

R³ is selected from the group consisting of alkyl, aryl, alleyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl; and one Y is -O- and the other Y is -NR⁶-.

171. (New) The compounds of claim 1, wherein:

W and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

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Response Serial No. 09/518,501 Page 9 of 110

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$ aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$ aryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V:

p is an integer 2 or 3;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

 R^{12} is selected from the group consisting of -H and lower acyl; one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), –N(lower alkylhalide)₂, or –N(lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.
 - 172. (New) The compounds of claim 1, wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

By

Response Serial No. 09/518,501 Page 10 of 110

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -CH₂aryl,

-CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C≡CR²)OH, -SR², and -CH₂NHaryl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

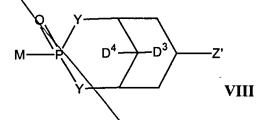
M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)₂, or -N(lower alkyl) (lower alkylhalide); and
 - R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

173. (New) The compounds of claim 1 that are of formula VIII:





10

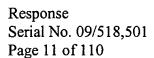
wherein:

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Z' is selected from the group consisting of -OH, -OCO₂R³, -OCOR³, and $-OC(O)SR^3$;

 R^2 is selected from the group consisting of R^3 and H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;



R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

 D^3 is -H;

D⁴ is selected from the group consisting of -H, alkyl, -OH, -OR² and -OC(O)R³.

M is selected from the group that attached to PO_3^{2-} , $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

Sub Cont

Please amend claims 1-3, 38, 42, 46, 48, 50, 58, 64, 70, 75, 81, 83, 85, 89, 93, 97, 101, 106-110, 112, 115, 118, 121, 124, 126, 131, 138, 141, 150, 151, 155, 161, 163-165 to read as indicated:

1. (Once amended) A compound of formula I:

B5

I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Response Serial No. 09/518,501 Page 13 of 110

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-R^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic; R^2 is selected from the group consisting of R^3 and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

 R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

 R^{12} is selected from the group consisting of -H, and lower acyl; one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.
- 2. (Once amended) The compounds of claim 1 wherein MP(O)(NHR⁶)O⁻, MPO₃²⁻, MP₂O₆³⁻, or MP₃O₉⁴⁻ is selected from the group consisting of an antiviral, anticancer, antihyperlipidemic, antifibrotic, and antiparasitic agent.





3. (Once amended) The compound of claim 1 wherein MP(O)(NHR⁶)O⁻, MPO₃²⁻, MP₂O₆³⁻, or MP₃O₉⁴⁻ is selected from the group consisting of metalloprotease inhibitor and TS inhibitor.

38. (Once amended) The compounds of claim 20 wherein said compound is of formula VI:

wherein

V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

42. (Once amended) The compounds of claim 20 wherein said compound is of formula VII:

VII



wherein

Z is selected from the group consisting of:

-CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OCO₂R³, -CHR²OC(O)SR³,

-CHR²OC(S)OR³, and -CH₂aryl.



46. (Once amended) The compounds of claim 20 wherein said compound is of formula VIII:

$$D^4$$
 D^3 D^3 D^4 D^3 D^3 D^4 D^3

Response Serial No. 09/518,501 Page 15 of 110

wherein

Z' is selected from the group consisting of -OH, -OC(O) \mathbb{R}^3 , -OCO₂ \mathbb{R}^3 , and -OC(O)S \mathbb{R}^3 ;

 D^3 is -H;

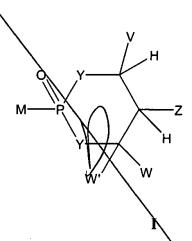
D⁴ is selected from the group consisting of -H, alkyl, -OH, and -OC(O)R³.

from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Z is selected from the group consisting of -H, OR², and -NHCOR².

50. (Once amended) The compounds of claim 49 wherein V is selected from the group consisting of phenyl and substituted phenyl.

58. (Once amended) A method of enhancing oral bioavailability of a parent drug by administering to an animal a compound of formula I:

by



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

Response Serial No. 09/518,501 Page 16 of 110

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V roust be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

 $-CHR^2OC(S)R^3, -CHR^2OC(S)OR^3, -CHR^2OC(O)SR^3, -CHR^2OCO_2R^3, -OR^2, -SR^2,$

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH $\stackrel{\longrightarrow}{=}$ CR²₂)OH, -CH(C $\stackrel{\longrightarrow}{=}$ CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCO₂R², -NHCO₂R³, -CH₂NHaryl, -(CH₂)_p-OR¹², and -(CH₂)_p-SR¹²;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

 R^2 is selected from the group consisting of R^3 and -N;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

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one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻, or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or -N(lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

64. (Once amended) The method of claim 63 wherein MPO₃²⁻, MP₂O₆³⁻, or MP₃O₉⁴⁻ is an antiviral or anticancer agent.

70. (Once amended) A method of delivering a biologically active drug to an animal for a sustained period by administering to an animal a compound of formula I:

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

Response Serial No. 09/518,501 Page 18 of 110

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together W and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and W must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH($CH = CR^2$)OH, -CH($C = CR^2$)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCO₂R³, -NHCO₂R², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

 R^2 is selected from the group consisting of R^3 and -N;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

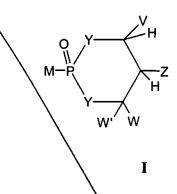


Response Serial No. 09/518,501 Page 19 of 110

with the provisos that:

- 1) M'iş not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

75. (Once amended) A method of delivering a biologically active drug to an animal with greater selectivity for the liver by administering to an animal a compound of formula I:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

Response Serial No. 09/518,501 Page 20 of 110

aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 beteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃², P₂O₆³-, P₃O₉⁴- or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

BY

B18

81. (Once amended) The method of claim 80 wherein said biologically active drug is FdUMP.

Byle

- 83. (Once amended) The method of claim 82 wherein the parent drug MPO₃²⁻ is selected from the group consisting of PMEA; PMEDAP; HPMPC, HPMPA; FPMEA; PMPA foscarnet, and phosphoracetic acid.
- 84. (Once amended) A method of increasing the therapeutic index of a drug by administering to an animal a compound of formula I:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

Response Serial No. 09/518,501 Page 22 of 110

aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C≡CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p$ -OR¹², and $-(CH_2)_p$ -SR¹²;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃², P₂O₆³, P₃O₉⁴ or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

BIR

89. (Once amended) A method of bypassing kinase resistance by administering to an animal a compound of formula I:

BY

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fixed to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

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Response
Serial No. 09/518,501
Page 24 of 110
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-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p$ -OR¹², and $-(CH_2)_p$ -SR¹²;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

018

93. (Once amended) The reflethod of claim 92 wherein MH is selected from the group consisting of F-ara-A, araC, CdA, dFac, and 5-fluoro-2'-deoxyuridine.

B19

97. (Once amended) A method of treating cancer expressing a P450 enzyme, by administering to an animal a compound of formula I:

BUT

Response Serial No. 09/518,501 Page 25 of 110

I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)CR^3$, $-CHR^2OC(S)C$, -CHCC, -CHCC, -CHCC, -CHCC, -

By

Page 26 of 110

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p - OR^{12}$, and $-(CH_2)_p - SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- V, Z, W, W' are not all -H; and
- when Z is R2, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic; b)

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is - NR^6 -:

M is selected from the group that attached to PO₃², P₂O₆³, P₃O₉⁴ or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- M is not -NH(lower alkyl), -N(lower alkyl), -NH(lower alkylhalide), 1)
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - R⁶ is not lower alkylhalide: 2)

and pharmaceutically acceptable prodrugs and salts thereof

101. (Once amended) The method of claim 97 wherein said compound is administered to patients resistant to the parent drug.

106. (Once amended) A raphod of treating liver fibrosis by administering to an animal-a compound of formula I:

Response Serial No. 09/518,501 Page 27 of 110

O Y - V H

M-P Y W' W

I

wherein:

V, W, and W are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH\$ $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C=CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CN₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;



p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

107. (Once amended) A method of treating hyperlipidemia by administering to an animal a compound of formula I:

wherein:

Response Serial No. 09/518,501 Page 29 of 110

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH= $\mathbb{C}\mathbb{R}^2_2$)OH, -CH(C= $\mathbb{C}\mathbb{R}^2$)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

 R^2 is selected from the group consisting of R^3 and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

BH ght

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R1 is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃², P₂O₆³, P₃O₉⁴ or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or -N(lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

108. (Once amended) The method of claim 107 wherein MPO_3^{2-} , $MP_2O_6^{3-}$, $MP_3O_9^{4-}$ or $MP(O)(NHR^6)O^-$ is a squalene synthase inhibitor.

B21

Response Serial No. 09/518,501 Page 31 of 110

(Once amended) A method of treating a parasitic infection by administering to an animal a compound of formula I:

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

 $-CHR^2OC(S)R^3, -CHR^2OC(S)OR^3, -CHR^2OC(O)SR^3, -CHR^2OCO_{\xi}R^3, -OR^2, -SR^2,$

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

Response Serial No. 09/518,501 Page 32 of 110

-OCO R^3 , -OCO₂ R^3 , -SCO R^3 , -SCO₂ R^3 , -NHCO R^2 , -NHCO₂ R^3 , -CH₂NHaryl, -(CH₂)_p-OR¹², and -(CH₂)_p-SR¹²;

p is an integer 2 or 3;

with the provisos that:

- a) $\bigvee V, Z, W, W'$ are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)₂, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

110. (Once amended) A method of delivering a diagnostic imaging agent to the liver comprising administering to an animal a compound of formula I:

wherein:

B2X

Response Serial No. 09/518,501 Page 33 of 110

W, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

 $-CHR^2OC(S)R^3, -CHR^2OC(S)OR^3, -CHR^2OO(O)SR^3, -CHR^2OCO_2R^3, -OR^2, -SR^2,$

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH= $\mathbb{C}\mathbb{R}^2_2$)OH, -CH(C= $\mathbb{C}\mathbb{R}^2$)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;



R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

 R^{12} is selected from the group consisting of -H, and lower acyl; one Y is O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, surface or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), –N(lower alkylhalide)₂, or –N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.

112. (Once amended) A method of treating a viral infection by administering to an animal a compound of formula I:

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

Response Serial No. 09/518,501 Page 35 of 110

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(\mathbb{CH} =CR²₂)OH, -CH(\mathbb{C} =CR²)OH, -R², -NR²₂,

 $-OCOR^3, -OCO_2R^3, -SCOR^3, -SCO_2R^{1\!\!\!/}, -NHCO_2R^3, -CH_2NHaryl,$

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO_3^{2-} , $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

Beef

Response Serial No. 09/518,501 Page 36 of 110

with the provisos that:

1) M'is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),

-N(lower alkylhalide), or -N(lower alkyl) (lower alkylhalide); and

2) R⁶ is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

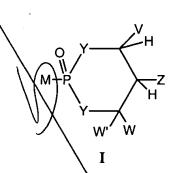
115. (Once amended) The method of claim 113 wherein said compound is administered to patients resistant to the parent drug.

118. (Once amended) The method of claim 112 wherein viral kinases produce M-PO₃².

121. (Once amended) A method of delivering a biologically active drug to target tissues comprising:

a) enhancing the activity of a P450 enzyme that oxidizes the compounds of formula I in said target tissues; and

b) administering to an animal a compound of formula I:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

Response Serial No. 09/518,501 Page 37 of 110

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(C=CR²₂)OH, -CH(C=CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-R^2$, then at least one of W, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³\and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

 R^{12} is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃², P₂O₆, P₃O₉⁴, or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

B26

Response Serial No. 09/518,501 Page 38 of 110

137/

with the provisos that:

1) Misnot -NH(lower alkyl), -N(lower alkyl)2, -NH(lower alkylhalide),

-N(lower alkylhalide)₂, or N(lower alkyl) (lower alkylhalide); and

2) R⁶ is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

124. (Once amended) The method of claim 121 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of endogenous P450 enzyme.

126. (Once amended) A method of treating tumor cells expressing a P450 enzyme comprising administering a cyclophosphamide analog selected from the group consisting of

R"R"'N P Y H

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

Response Serial No. 09/518,501 Page 39 of 110

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

 $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH - H(CH=CR²₂)OH, -CH(C=CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶⁶ is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

R¹² is selected from the group consisting of -H, and lower acyl;

R" is lower 2-haloalkyl;

R" is selected from the group consisting of H, lower alkyl, and R";

one Y is -O- and the other Y is -NR⁶⁶-;

and pharmaceutically acceptable prodrugs and salts thereof.

131. (Once amended) The method of claim 127 wherein the activity of a P450 enzyme is enhanced by administration of a compound that increases the amount of endogenous P450 enzyme.

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- 138. (Qnce amended) A method of treating tumor cells comprising
 - a) \ enhancing the activity of a P450 enzyme that oxidizes cyclophosphamide analogs;
 - b) \administering to an animal a cyclophosphamide analog selected from the group

consisting of:

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

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Response
Serial No. 09/518,501
Page 41 of 110
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together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

Z is selected from the group consisting of -CHR OH, -CHR OC(O)R,

 $-CHR^2OC(S)R^3, -CHR^2OC(S)OR^3, -CHR^2OC(O)SR^3, -CHR^2OCO_2R^3, -OR^2, -SR^2, -CHR^2OCO_2R^3, -OR^2, -O$

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C \equiv CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p - OR^{12}$, and $-(CH_2)_p + R^{1}$;

p is an integer 2 or 3,

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶⁶ is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

R¹² is selected from the group consisting of -H, and lower acyl;

R" is lower 2-haloalkyl;

R" is selected from the group consisting of H, lower alkyl, and R";

one Y is -O- and the other Y is -NR⁶⁶-

and pharmaceutically acceptable prodrugs and salts thereof.

141. (Once amended) The method of claim 138 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of endogenous P450 enzyme.

150. (Once amended) A method of making a compound of Formula I comprising,

a) transforming a drug having a - PO₃²⁻ or -P(O)(NHR⁶)O moiety into a compound of formula I:



Response Serial No. 09/518,501 Page 42 of 110

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

 $\label{eq:Z} Z \ is \ selected \ from \ the \ group \ consisting \ of -CHR^2OH \ , \ -CHR^2OC(O)R^3, \ -CHR^2OC(S)R^3, \ -CHR^2OC(S)R^3, \ -CHR^2OC(O)SR^3, \ -CHR^2OCO_2R^3, \ -OR^2 \ , \ -SR^2, \ -OR^2 \ , \ -O$

-CHR 2 N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR 2 ₂)OH, -CH(C \equiv CR 2)OH, -R 2 , -NR 2 ₂,

B31

Response Serial No. 09/518,501 Page 43 of 110

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl, $-(CH_2)_p - OR^{12}$, and $-(CH_2)_p - SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- V, Z, W, W' are not all -H; and
- when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic; b)

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl; one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻, or P(O)(NHR⁶)O is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - R⁶ is not lower alkylhalide: 2)

and pharmaceutically acceptable prodrugs and salts thereof.

- 151. (Once amended) The method of claim 150 further comprising,
- converting M-PO₃² to a compound M-P(O)L"₂ wherein L" is a halogen; and a)
- reacting M-P(O)L"₂ with HY-CH(V)CH(Z)-CW(W')-YH. b)

(Once amended) The method of claim 166 wherein L-P(-YCH(V)CH(Z)-CW(W')Y-) is chiral.

(Once amended) A compound, N-P-(-YCH(V)CH(Z)-CW(W')Y-) wherein:

Response Serial No. 09/518,501 Page 44 of 110

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$ aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCO_2R^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$ aryl, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W'\is not -H, alkyl, aralkyl, or alicyclic;



Response Serial No. 09/518,501 Page 45 of 110

each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom;

R² is selected from the group consisting of R³ and -H;

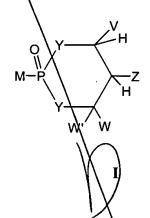
R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

 R^{12} is selected from the group consisting of -H, and lower acyl; one Y is -O- and the other Y is -NR⁶-; with the proviso that R^1 is not methyl.

163. (Once amended) A method of delivering a compound to hepatocytes wherein said compound has a moiety selected from the group consisting of phosph(on)ate comprising:

a) converting said compound to a compound of formula I:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

Response Serial No. 09/518,501 Page 46 of 110

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and Ware connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(C=CR²₂)OH, -CH(C=CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

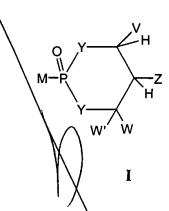
M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

1339 of Response Serial No. 09/518,501 Page 47 of 110

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide; and pharmaceutically acceptable prodrugs and salts thereof.
- 164. (Once amended) A method of enhancing the pharmacodynamic half-life of a parent drug by administering to an animal a compound of formula I:





wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

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Response
Serial No. 09/518,501
Page 48 of 110
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aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³,

-CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR²,

-CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²₂)OH, -CH(C≡CR²)OH, -R², -NR²₂,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl,

 $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all H; and

b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not –NH(lower alkyl), -N(lower alkyl)₂\,-NH(lower alkylhalide),
- -N(lower alkylhalide)2, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.



Response Serial No. 09/518,501 Page 49 of 110

1334 cut 165. (Once amended) The compounds of claim 1 wherein V and M are *cis* to one another on the phosphorus-containing ring of Formula I.